

# Sporadic late-onset nemaline myopathy with MGUS

## Long-term follow-up after melphalan and SCT



Nicol C. Voermans, MD,  
PhD  
Olivier Benveniste, MD,  
PhD  
Monique C. Minnema,  
MD, PhD  
Henk Lokhorst, MD,  
PhD  
Martin Lammens, MD,  
PhD  
Wouter Meersseman,  
MD, PhD  
Michel Delforge, MD,  
PhD  
Thierry Kuntzer, MD  
Jan Novy, MD  
Thomas Pabst, MD  
Françoise Bouhour, MD  
Norma Romero, MD,  
PhD  
Veronique Leblond, MD  
Peter van den Bergh, MD,  
PhD  
Marie-Christiane  
Vekemans, MD  
Baziel G. van Engelen,  
MD, PhD\*  
Bruno Eymard, MD,  
PhD\*

Correspondence to  
Dr. Voermans:  
nicol.voermans@radboudumc.nl

Supplemental data  
at [Neurology.org](#)

### ABSTRACT

**Objective:** Sporadic late-onset nemaline myopathy (SLONM) is a rare, late-onset myopathy that progresses subacutely. If associated with a monoclonal gammopathy of unknown significance (MGUS), the outcome is unfavorable: the majority of these patients die within 1 to 5 years of respiratory failure. This study aims to qualitatively assess the long-term treatment effect of high-dose melphalan (HDM) followed by autologous stem cell transplantation (SCT) in a series of 8 patients with SLONM-MGUS.

**Methods:** We performed a retrospective case series study (n = 8) on the long-term (1–8 years) treatment effect of HDM followed by autologous SCT (HDM-SCT) on survival, muscle strength, and functional capacities.

**Results:** Seven patients showed a lasting moderate-good clinical response, 2 of them after the second HDM-SCT. All of them had a complete, a very good partial, or a partial hematologic response. One patient showed no clinical or hematologic response and died.

**Conclusions:** This case series shows the positive effect of HDM-SCT in this rare disorder. Factors that may portend an unfavorable outcome are a long disease course before the hematologic treatment and a poor hematologic response. Age at onset, level and type of M protein ( $\kappa$  vs  $\lambda$ ), and severity of muscle weakness were not associated with a specific outcome.

**Classification of evidence:** This study provides Class IV evidence that for patients with SLONM-MGUS, HDM-SCT increases the probability of survival and functional improvement. *Neurology*® 2014;83:2133–2139

### GLOSSARY

**HDM** = high-dose melphalan; **MGUS** = monoclonal gammopathy of unknown significance; **SCT** = stem cell transplantation; **SLONM** = sporadic late-onset nemaline myopathy.

Sporadic late-onset nemaline myopathy (SLONM) is a rare, late-onset myopathy that progresses subacutely. Limb-girdle and axial weakness and atrophy predominate the clinical picture. Distal weakness, head drop, respiratory insufficiency, and dysphagia can also occur.<sup>1,2</sup> Patients may be suspected to have motor neuron disease because of the rapid course and severe atrophy. Recognition of nemaline rods on trichrome and  $\alpha$ -actinin staining or electron microscopy is crucial.

SLONM is in a significant proportion of cases associated with a monoclonal gammopathy of unknown significance (MGUS), a combination that portends an unfavorable outcome: the majority of these patients die within 1 to 5 years of respiratory failure.<sup>3</sup> In 2008, our 2 groups concurrently but independently reported the effective treatment of 2 patients with SLONM associated with MGUS (SLONM-MGUS) with high-dose melphalan (HDM) followed by autologous stem cell transplantation (SCT). Both patients showed significant increase of muscle

\*These authors contributed equally to this work.

From the Departments of Neurology (N.C.V., B.G.v.E.) and Pathology (M.L.), Radboud University Medical Centre, Nijmegen, the Netherlands; Department of Internal Medicine (O.B.), Hôpital Pitié Salpêtrière, UPMC, U974, DHU I2B, Paris, France; Department of Hematology (M.C.M., H.L.), University Medical Center Utrecht, the Netherlands; Department of Pathology (M.L.), Antwerp University Hospital, University of Antwerp, Edegem; Departments of Internal Medicine (W.M.) and Hematology (M.D.), University Hospital Leuven, Belgium; Neurology Service (T.K., J.N.), Lausanne University Hospital CHUV, Lausanne; Department of Medical Oncology (T.P.), University Hospital Bern, Switzerland; Electromyography and Neuromuscular Pathologies Department Lyon Est (F.B.), Bron Hospitals, France; Departments of Pathology (N.R.) and Neurology (B.E.), Hôpital Pitié Salpêtrière, Myology Institute, Paris; Department of Hematology (V.L., P.v.d.B.), Hôpital Pitié Salpêtrière, UPMC Univ Paris 6 GRC 11 GRECHY, Paris, France; Neuromuscular Reference Centre, Department of Neurology (V.L., P.v.d.B.), and Department of Hematology (M.C.V.), Cliniques Universitaires Saint-Luc, University of Louvain, Brussels, Belgium.

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**Table 1** Main features of the myopathy in 8 patients with SLONM and MGUS

	Patient							
	1	2	3	4	5	6	7	8
<b>Sex</b>	M	M	F	F	F	F	M	F
<b>Age at onset, y</b>	38	59	47	63	60	39	54	36
<b>Symptoms at onset</b>	Proximal upper > lower limb weakness	Proximal upper and lower limb weakness	Proximal lower limb weakness	Proximal lower limb weakness	Proximal lower limb weakness	Upper and lower girdles weakness, neck weakness	Proximal lower limb weakness	Limb-girdle weakness and pain
<b>Age at diagnosis, y</b>	40	61	49	64	66	44	55	38
<b>Treatment before diagnosis</b>	Prednisone	None	Laminectomy	None	None	Methotrexate, prednisolone, IVIg, plasma exchanges, rituximab	None	Methylprednisolone, plasma exchange
<b>CK, U/L (normal &lt;414 U/L for males; &lt;217 for females)</b>	167	238	150	160	65	Normal	170	133
<b>EMG</b>	Myopathic, fast recruitment	Myopathic and neurogenic	Myopathic	Myopathic	Myopathic	Myopathic	Myopathic	Polyphasic MUPs in proximal muscles
<b>Muscle biopsy/biopsies (site)</b>	1st (VL): neurogenic changes, secondary myopathic changes; reevaluation 1st: nemaline rods	1st (VL): neurogenic changes, secondary myopathic changes; 2nd (VL): nemaline rods	1st (VL): COX-deficient fibers but no EM signs of mitochondrial myopathy; 2nd (VL): nemaline rods	1st (D): type 1 fiber atrophy; 2nd (D): nemaline rods	1st (VL): no inflammation neither vacuoles; 2nd (VL): atrophic and lobulated fibers; 3rd (VL): nemaline rods	1st and 2nd (D): atrophic fibers; 3rd (BB): pseudo-perifascicular atrophy; 4th (VL): nemaline rods	Atrophic fibers and nemaline rods (D)	1st (D): normal; 2nd (VL): nemaline rods
<b>EM</b>	Nemaline rods	Nemaline rods	Nemaline rods	Nemaline rods	ND	Nemaline rods	Nemaline rods	Nemaline rods
<b>Age at moment of the SCT, y</b>	40	61	50	66	71	44	56	39
<b>Symptoms at the moment of the SCT</b>	Severe weakness affecting proximal arms > legs, and neck extensors (head drop); winging of scapula	Severe weakness affecting proximal arms > legs, and winging of scapula	Severe weakness affecting proximal arms and legs, and winging of scapula	Lower limbs weakness ↑; proximal upper limbs + axial weakness	Severe weakness affecting proximal limbs, trunk flexors, and neck extensors (head drop)	Myalgia, severe weakness affecting proximal limbs, trunk flexors, and neck extensors (head drop)	Severe weakness affecting proximal legs > arms and neck extensors	Severe proximal weakness, including axial muscles with head drop
<b>Walking</b>	Walking independently	Walking with a cane	Walking with walker or with partner	Some steps with help; WCB for 2 y	Walking at home with walker	WCB	Waddling gait; later WCB	WCB
<b>Bulbar weakness</b>	Mild dysarthria and dysphagia	Mild dysarthria and dysphagia	Dysphagia	No	No	No	Mild	Severe dysphagia (PEG)
<b>Facial weakness (incomplete eye closure or reduced touting of lips)</b>	Mild	Mild	Mild	No	No	No	Mild	Mild
<b>Respiratory weakness</b>	No	No	No	No	No	Yes: VC ↓ 40%	Mild	Yes: VC ↓ 54%

Abbreviations: BB = biceps brachii muscle; CK = creatine kinase; COX = cyclooxygenase; D = deltoid muscle; EM = electron microscopy; IVIg = IV immunoglobulin; MGUS = monoclonal gammopathy of unknown significance; MUP = motor unit potential; ND = not determined/not documented; PEG = percutaneous endoscopic gastrostomy; SCT = stem cell transplantation; SLONM = sporadic late-onset nemaline myopathy; VC = vital capacity; VL = vastus lateralis muscle; WCB = wheelchair bound.

**Table 2** Response to HDM with autologous SCT

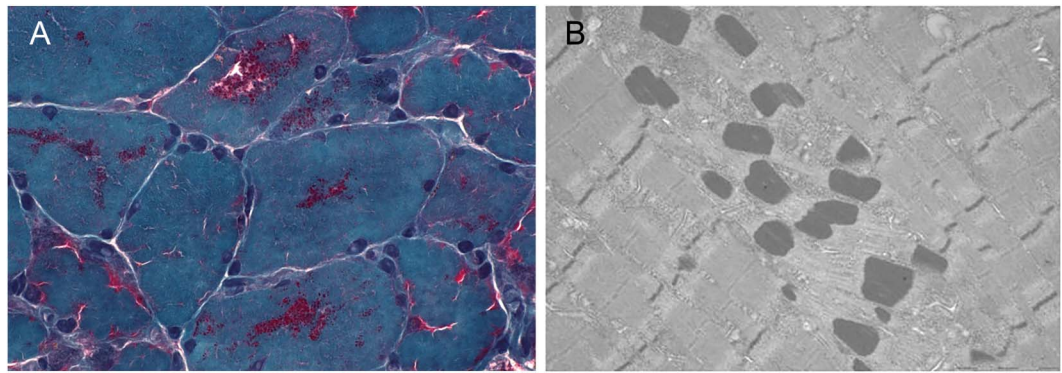
	Patient									
	1	2	3	4	5	6	7	8		
	After 1st graft	After 2nd graft					After 1st graft	After 2nd graft		
<b>Neurologic features</b>										
Age at onset, y	38	40	59	47	63	60	39	46	54	36
Duration before SCT, y	2		2.5	2	2	11	5		2	3
Follow-up after graft	4 y	3.5 y	4 y	2.5 y	8 y	5 y	2.5 y	4 mo	6 y	12 mo
Limb weakness UL: 0 to +++ before/after graft	+++ / ++	+++ / ++	+++ / ++	+++ / ++	+++ / +	+++ / +++	+++ / +++	+++ / +++	+++ / ++	+++ / ++
Limb weakness LL: 0 to +++ before/after graft	++ / +	++ / +	++ / +	++ / +	+++ / +	+++ / +++	+++ / +++	+++ / ++	+++ / ++	+++ / ++
Arm abduction before/after graft, °	20/45	30/45	ND/70 (R) 60 (L)	40 (R) 30 (L)/60	45/150	40/30	30/2 y: 60; 2.5 y: worsened	0/40	20/90	0/20
Walk assistance before/after graft	Walking unaided/running	Walking unaided/running	Walking with cane/walking with cane (longer distance and higher speed)	Walking with walker/walking with cane	WCB for outside, walker at home/walk unaided	WCB outside, walker at home/bedridden	WCB continuously/ from 3rd mo to 2 y: walks 10 m, alone. Thereafter worsening: permanent WCB	WCB/WCB (distal LL recovery)	Walking with walker/walk unaided	WCB/WCB but walking a few meters with walker
Walton CSS before/after graft	1/2	1/2	6/4	6/4	7/2	6/10	7/ from 3rd to 24th mo 6; after 7	7/8	9/3	9/8
Brooke scale before/after graft	4/2	3/2	4/2	ND/ND	4/2	ND/ND	ND/ND	ND/ND	5/2	5/4
Facial, bulbar, respiratory involvement before/after graft	Yes, yes, no/no, no, no	ND/no, no, no	Yes, yes, no/no, no, no	Yes, yes, no/no, no, no	No, no, no/no, no, no	No, no, yes/no, no, no	No, no, yes/no, no, ND	No, no, ND/no, yes, yes aspiration pneumonia	No, no, yes/yes, no, no	Yes/no
Head drop before/after graft	Severe/mild	Severe/mild	No/no	Yes/no	Yes/no	Yes/yes	Yes/yes	Yes/yes	Mild/no	Yes/no
<b>Hematologic features</b>										
M protein	IgG κ		IgG λ	IgG λ	IgG λ	IgG κ	IgG λ		IgG κ	IgG κ
M protein level before graft, g/L	7.4	0.1	Detectable but unquantifiable	3.3	2.6	2.6	9.4 (20 mo before); detectable but unquantifiable (3 mo before)	17.8	11	0.24
M protein level after graft, g/L; last examination	0; 3.0 at 3 y 9 mo	Detectable but unquantifiable	Detectable but unquantifiable; 0 after lenalidomide	Detectable but unquantifiable	0	5.8	0; 17.8 at 2 y	5.6	Detectable but unquantifiable at 6 mo, then 0 at 6 y	0

Continued

Table 2 Continued

	Patient									
	1		2	3	4	5	6		7	8
	After 1st graft	After 2nd graft					After 1st graft	After 2nd graft		
Bone marrow biopsy before graft	10%–20% monoclonal plasma cells		1% monoclonal plasma cells	<5% monoclonal plasma cells; immunophenotyping: 0.43% plasma cells, of which 0.27% monoclonal	4% monoclonal plasma cells	4.5 y before graft: 8% monoclonal plasma cells; 4 mo before, rich bone, 0% plasma cells	4.5 y before graft: hypoplasia, no abnormal infiltration; 4 mo before graft: 2% monoclonal plasma cells		5%–10% monoclonal plasma cell	Normal
Therapies before graft: PE, IVIg, steroids, cytostatics, melphalan (just before graft)	Prednisone, melphalan	IVIg, rituximab, melphalan	Melphalan	Melphalan	Melphalan	PE, dexamethasone, cyclophosphamide, Alkeran, melphalan	PE, IVIg, prednisolone, methotrexate, rituximab, melphalan	Melphalan	Melphalan	Methylprednisolone, PE
Therapies after graft		Lenalidomide (10 mg daily 21/28 d)	Lenalidomide (10 mg lenalidomide 21/28; dexamethasone (40 mg weekly)	Lenalidomide (25 mg daily 21/28 d); dexamethasone (20 mg weekly) up to 2.5 y after SCT	None	Lenalidomide; dexamethasone (started 2 y after SCT); dose ND	None	None	None	None
Summary of treatment response										
M protein	IgG κ		IgG λ	IgG λ	IgG λ	IgG κ	IgG λ		IgG κ	IgG κ
M protein level before graft, g/L	7.4	0.1	n.q.	3.3	2.6	2.6	9.4; n.q. (after treatment)	17.8	11	0.24
Follow-up after graft	4 y	3.5 y	4 y	2.5 y	8 y	5 y	2.5 y	8 mo	6 y	12 mo
Clinical response	II	I	I	I	I	IV	II	I	I	I
Hematologic response	CR (3 y 9 mo); PD after that	VGPR	CR	VGPR	CR	PD	CR (2 y); PD after that	PR	CR	CR

Abbreviations: CR = complete response; CSS = clinical severity score; HDM = high-dose melphalan; IgG = immunoglobulin G; IVIg = IV immunoglobulin; LL = lower limb; ND = not determined/not documented; PD = progressive disease; PE = plasma exchange; PR = partial response; SCT = stem cell transplantation; SD = stable disease; UL = upper limb; VGPR = very good partial response; WCB = wheelchair bound. The hematologic response to the HDM with SCT and to other chemotherapy was classified according to international criteria (International Myeloma Working Group uniform response criteria)<sup>11</sup>: CR = no M protein in serum and urine and ≤5% plasma cells in bone marrow; VGPR = M protein only detectable on electrophoresis or ≥90% reduction of M protein in serum; PR = ≥50% reduction of serum M protein and ≥90% reduction of 24-hour urine M protein; SD = no response; PD = increase of >25% from lowest response value in any M protein level. Muscle strength was assessed with manual muscle testing (Medical Research Council [MRC] scores 0–5), and muscle weakness was subsequently classified as 0 (MRC 5 in muscles of UL/LL); + (MRC 4); ++ (MRC 3); or +++ (MRC 0–1–2). To evaluate the effect of HDM and SCT on the disease course, the overall clinical response was classified as: (I) lasting moderate–good response (increase of muscle strength of at least 2 muscle groups on manual muscle testing [MMT] and any functional improvement during follow-up); (II) temporarily moderate–good (initial increase of muscle strength of at least 2 muscle groups on MMT and any functional improvement with secondary decrease of muscle strength of at least 2 muscle groups on MMT or functional loss during follow-up); (III) poor (no increase of muscle strength of at least 2 muscle groups on MMT or not any functional improvement but slowing of the pretreatment clinical deterioration); and (IV) no response (no alteration of the pretreatment disease course).



Quadriceps biopsy showing numerous rods in Gomori trichrome staining (A) and on electron microscopy (B).

strength and functional improvement up to independent walking and even running in one.<sup>4,5</sup> The editorial rightly commented that the duration of follow-up (15–24 months) was short, and suggested the possible effectiveness of alternative, safer therapies, such as thalidomide or lenalidomide.<sup>6</sup> Since then, only 4 other SLONM-MGUS patients have been reported in the literature, with similar treatment responses on HDM-SCT in 2 of them.<sup>7–9</sup>

This retrospective case series aims to assess the long-term treatment response of HDM followed by autologous SCT (HDM-SCT) in 8 patients with SLONM-MGUS.

**METHODS** Methods of clinical, hematologic, and histopathologic data collection, definitions of clinical and hematologic treatment response, and information on patient consents are listed in appendix e-1 on the *Neurology*<sup>®</sup> Web site at [Neurology.org](http://Neurology.org).

**RESULTS** The clinical response to treatment varied from long-lasting moderate to good for 7 patients (I: patients 1 [second HDM-SCT], 2, 3, 4, 6 [second HDM-SCT], 7, and 8), to temporarily moderate–good in 2 patients who subsequently received a second HDM-SCT (II: patients 1 and 6), and no response (IV: patient 5). In parallel, the hematologic responses diverged from complete response (patients 1 [first HDM-SCT], 2, 4, 6 [first HDM-SCT], 7, and 8), very good partial response (patients 1 [second HDM-SCT] and 3), partial response (patient 6 [second HDM-SCT]), to progressive disease (patient 5). This latter patient showed neither a clinical nor a hematologic response and died. For patient 6, the period after the second HDM-SCT was particularly difficult because of a severe aspiration pneumonia, requiring intensive care management including tracheostomy and gastrostomy, but a significant improvement gradually started after 3 months. Patient 8 was in very poor shape with

significant weight loss and swallowing problems when she entered the hospital for SCT. She developed bilateral aspiration pneumonia and had to be intubated, requiring the HDM-SCT to be postponed. Table 1 presents the main features of the myopathy, and table 2 shows the responses to treatment. The individual case histories of the 8 patients are added as appendix e-2 (figure).

The only completely unresponsive patient (patient 5) differed from the other patients for the following characteristics: a particularly long duration before the autologous HDM-SCT (11 years) and no hematologic response after HDM. In the 2 patients with only a temporary response to treatment (patients 1 and 6), the delay before the graft was variable: 2 and 5 years, respectively. In the first patient, muscle weakness recurred in parallel with a reappearance of M protein, although at a much lower level than before (0.1 g/L against 7.4 g/L before first graft), probably related to higher awareness and regular measurements. In patient 6, the clinical worsening 2 years after the graft was also associated with a large increase of M protein (17.8 g/L against 9.4 g/L before first graft). Age at onset of muscle weakness, severity of muscle weakness before HDM-SCT, and the level and type of M protein and results of bone marrow aspiration before the graft did not correlate with the clinical response.

Lastly, 4 patients were treated after HDM-SCT with lenalidomide to prevent a hematologic relapse after HDM-SCT or to induce a (unsuccessful) hematologic response in the patient with stable disease after treatment. However, 2 other patients remained in complete response after HDM-SCT without the use of lenalidomide so the value of adding this drug cannot be ascertained.

**DISCUSSION** This case series shows the long-term follow-up of 8 patients with SLONM-MGUS after treatment with HDM-SCT. Seven patients showed a lasting moderate–good clinical response (2 of which only after the second treatment), 6 with a very good



partial or complete hematologic response, and one with a partial hematologic response. One patient showed no clinical or hematologic response and died. Factors that may portend an unfavorable clinical outcome are a long disease course before HDM-SCT and a poor hematologic response to treatment. Age at onset, level and type of M protein, and severity of muscle weakness before the graft were not associated with outcome. This underlines the importance of early recognition of this disorder by M protein screening and (repeated) muscle biopsies in clinically suspected cases. Timely diagnosis will also enable start of treatment when the patient is still in a relatively good clinical condition.

The limitations of this case series are that it is a retrospective study, the number of patients is limited, and treatment is not blinded. However, it is the first long-term follow-up of a series of SLONM-MGUS patients treated with HDM-SCT and undoubtedly shows the positive treatment response with a follow-up of 9 months to 8 years in this otherwise fatal disease.

SLONM pathophysiologic mechanisms are unknown, but several observations are suggestive of an association between the (level of) the M protein and the disorder<sup>4,5</sup>: appearance of rods later in the course of the disease (which in this series is unlikely to be due to sampling error); responsiveness to anti-plasma cell chemotherapy; disappearance of nemaline rods after treatment; increase of the M protein level preceding clinical deterioration; and the absence of a hematologic response to HDM-SCT paralleling the lack of clinical improvement in patient 5. The disease may therefore be classified as an MGUS with a toxic M protein similar to POEMS (polyneuropathy, organomegaly, endocrinopathy/edema, M protein, skin abnormalities) syndrome. Here, not the aggregation and deposition of the monoclonal antibodies in affected tissue but the antibody activity toward autogenous antigens, possibly augmented by other humoral mediators, is considered causative.<sup>10</sup> This and other MGUS with a toxic M protein-like disorder show a similar response after HDM-SCT as observed in this SLONM-MGUS series. This calls for further investigations in the exact role of the M protein in SLONM-MGUS.

Based on this series and the experience in management of other hematologic diseases with dangerous B-cell clones, we suggest that HDM-SCT should be the first-line therapy for SLONM-MGUS: first, the natural course of SLONM-MGUS is fatal; second, the goal of treatment should be to suppress the clone as soon as possible to reduce the monoclonal protein and its toxic effects; third, treatment is preferably started when the patient is still in a relatively good clinical condition. Furthermore, because the severity of SLONM is likely to be correlated to the quantity and/or quality of the toxic M protein after HDM-

SCT, consolidation and maintenance therapy may be considered to achieve and maintain an optimal hematologic response.

In short, this retrospective SLONM-MGUS case series on the long-term follow-up shows that the probability of survival, muscle strength, and functional capacities improve after treatment with HDM-SCT (class IV evidence). Factors associated with positive benefit of HDM-SCT in SLONM-MGUS are shorter duration between onset of symptoms and treatment and a good hematologic response to treatment. This again underscores the importance of early recognition of this rare, acquired myopathy.

## AUTHOR CONTRIBUTIONS

Nicol Voermans: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Olivier Benveniste: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. M. Minnema: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. H. Lokhorst: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, patient treatment. M. Lammens: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval. W. Meersseman: analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. M. Delforge: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. T. Kuntzer: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data, statistical analysis, study supervision. T. Pabst: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, contribution of vital reagents/tools/patients, acquisition of data. F. Bouhour: study concept or design, accepts responsibility for conduct of research and will give final approval, acquisition of data. N. Beatriz Romero: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval. V. Leblond: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and will give final approval, acquisition of data. Peter Van den Bergh: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. M. Vekemans: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. B. van Engelen: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. B. Eymard: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision.

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